In This Issue

Cell

An Energy Boost from Resveratrol

PAGE 1109

Resveratrol is a natural polyphenolic compound that extends life span in many species by poorly understood mechanisms. Now Lagouge et al. find that resveratrol treatment results in improved mitochondrial function, aerobic capacity, and metabolic homeostasis in mice. Given that resveratrol activates the SIRT1 protein deacetylase, these effects were largely explained by a SIRT1-mediated decrease in PGC-1 acetylation, resulting in the enhanced activity of this mitochondrial coactivator. The association of three *Sirt1* genetic polymorphisms with altered energy expenditure in humans extends the impact of these observations from mice to men and implicates SIRT1 as a key regulator of energy and metabolic homeostasis.

Hope for a Broken Heart

PAGE 1137 and PAGE 1151

The heart contains three major lineages—myocardial, smooth muscle, and endothelial cells—that are thought to arise from distinct embryonic precursors. Wu et al. found, unexpectedly, that cardiomyocytes and smooth muscle cells share a common origin. Using embryonic stem cells, Moretti et al. clonally amplified cardiovascular progenitors and determined the transcriptional signature of a "master" cardiovascular stem cell that can give rise to the three cell lineages. These studies suggest a new strategy for cardiovascular tissue regeneration via isolation, renewal, and directed differentiation of master cardiovascular stem cells into specific cardiac, pacemaker, smooth muscle, and endothelial cell types.

TRPing up Diabetes

PAGE 1123

In Type 1 diabetes, pathogenic lymphocytes infiltrate pancreatic islets and mediate β cell death resulting in insulin deficiency. However, what attracts or restricts broadly autoreactive lymphocyte pools to the pancreas remains unclear. Razavi et al. demonstrate that insulin-responsive pancreatic sensory neurons that express TRPV1 regulate access to inflammatory tissue by controlling the release of neuropeptides such as substance P. Eliminating these neurons or enhancement of pancreatic substance P levels in diabetes-prone NOD mice normalizes insulin resistance, clears inflammation, and prevents diabetes, despite systemic persistence of pathogenic T cell pools. These data uncover a fundamental role for insulin-responsive $TRPV1^+$ sensory neurons in β cell function and diabetes pathoetiology.

Getting by with One Holliday

PAGE 1167

Meiotic recombination can be initiated by DNA double-strand breaks. These breaks were postulated to be repaired via a joint intermediate in which two parental strands are connected by two Holliday junctions. Such double Holliday junctions—observed in budding yeast—were thought to be a universal intermediate of mitotic and meiotic double-strand breaks repair. Cromie et al. report that most fission yeast meiotic joint intermediates contain single, not double, Holliday junctions. In further contrast with budding yeast, these joint molecules arise more frequently between sister chromatids than between homologs. These results reveal unexpected mechanistic differences in a fundamental process such as meiosis.

Resolving Tension at the Centromere

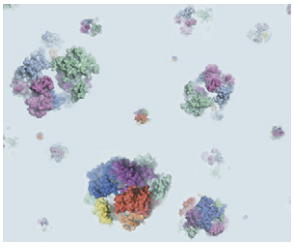
PAGE 1179

Sandall et al. use a biochemical assay based on the simple budding yeast centromere to identify a complex of two conserved chromosomal passenger proteins (Bir1-Sli15, known as Survivin-INCENP in metazoans) that links centromeres to spindle microtubules. The linkage mediated by this complex is not required for core centromere-microtubule attachment in vivo. However, it is critical for tension-dependent control of centromere-microtubule interactions by Aurora B kinase, which corrects improper connections between centromeres and the spindle microtubules. The authors propose that the Bir1-Sli15-mediated linkage acts as a tension-sensitive regulator of Aurora B activity.

Exosome Exposé

PAGE 1223

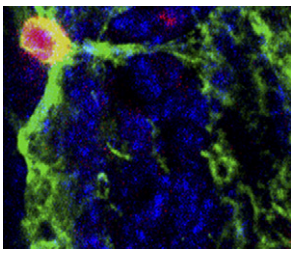
The RNA exosome, a multisubunit 3′ to 5′ exoribonuclease complex, participates in RNA processing and degradation. Here Liu et al. reconstituted exosomes from individual yeast and human subunits, facilitating biochemical comparison with different RNA substrates. These studies revealed substrate preferences and differences in enzymatic activity within the subunits of human and yeast exosomes. Furthermore, the authors determined the crystal structure for the nine-subunit human exosome, elucidating the architecture of a eukaryotic exosome and the structural basis for exosome activities.



21U-RNAs, in a Class of Their Own

PAGE 1193

Small RNAs regulate gene expression and developmental progression in many eukaryotes. Ruby et al. use high-throughput sequencing to perform an in-depth survey of small RNAs expressed in *C. elegans*. In addition to identifying new microRNAs and many siRNAs, they discovered 21U-RNAs, an abundant class of diverse, autonomously expressed, small RNAs that originate from thousands of loci scattered across several broad regions of chromosome IV. These loci share an upstream motif that is conserved in other nematodes.



Numbing the Effects of Brain Ventricular Wall Damage

PAGE 1253

Neural stem cells are retained in special areas of the postnatal mammalian brain, such as the subventricular zone. Here, Kuo et al. generated a mouse model in which Numb/Numblike—critical regulators of neuroprogenitor differentiation—were genetically removed postnatally from the subventricular zone neurogenic niche. Absence of Numb affected the integrity of the lateral ventricle, but over time the damaged wall was repaired by progenitors that had escaped Numb deletion. The experiments reveal a surprising capacity of neural stem cells to participate in tissue repair.

Transcriptional Interference Represses Hox Gene

PAGE 1209

Long noncoding RNAs are common in eukaryotes, but their functions are poorly understood. The noncoding RNAs of the bithorax complex (part of the Hox gene cluster) of *Drosophila* have been proposed to activate transcription of coding genes. Petruk et al. now show that in the bithorax complex, transcription of noncoding RNAs occurs primarily in cells that do not express the Hox gene *Ubx*, and that the transcription acts in cis to repress *Ubx*. Furthermore, the noncoding RNAs are elongated by the Trithorax complex TAC1. These exciting results suggest that transcription of noncoding RNAs represses Ubx expression by transcriptional interference.

PP2A, the Holo Story

PAGE 1239

The protein serine/threonine phosphatase PP2A is a heterotrimeric holoenzyme that consists of three subunits: scaffolding, catalytic, and regulatory. Xu et al. solve the crystal structure of the holoenzyme to reveal how these subunits are assembled. They show that the regulatory subunit B′/B56/PR61 has a structure similar to that of the scaffolding subunit. B′/B56/PR61 simultaneously interacts with the other two subunits and induces a pronounced conformational rearrangement in the scaffolding subunit upon assembly of the holoenzyme. This structure serves as an important framework for understanding PP2A function and regulation.

'Oming in on the Secretory Pathway

PAGE 1265

Gilchrist et al. use quantitative proteomics to provide insight into proteins of the mammalian secretory pathway. The authors identify more than 1400 proteins in the secretory pathway. They also spatially determine where these proteins are present in secretory compartments such as COPI vesicles, Golgi cisternae, and rough and smooth endoplasmic reticulum. The data indicate a role for COPI vesicles in cargo recycling and support a cisternal maturation model of Golgi formation. Furthermore, their proteomic strategy may be useful to determine the components of other pathways.